

**PATENT APPLICATION
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re application of

Takumi TAKEYASU, et al.

Appln. No.: 10/574,688

Group Art Unit: 1609

Filed: April 5, 2006

Examiner: Robert Havlin

For: A METHOD FOR PRODUCING AMINOPYRROLIDINE DERIVATIVES AND
INTERMEDIATE COMPOUNDS

DECLARATION UNDER 37 C.F.R. § 1.132

Commissioner for Patents
Alexandria, Virginia 22313-1450

Sir:

I, Takumi Takeyasu, hereby declare and state:

THAT I am a citizen of Japan;

THAT I have received a Masters Degree in 1988 from Osaka University;

THAT I am a member of several Japanese Scientific Societies related to research in Medicinal
Chemistry and Process Chemistry.

THAT I have been employed by Teijin Pharma Ltd. (former Teijin Ltd.) since 1988.

THAT I was in the Medicinal Chemistry Research Department, where I involved in the drug
discovery research.

THAT I am in the Pharmaceutical Products Research Department, where I have involved in the
process chemistry research for drug substances.

I have thorough knowledge of the invention in the above-referenced patent application and I have read the
non-final Office Action of May 29, 2007 issued in reference to the application. In response to the non-
final Office Action, I submit herewith this Declaration demonstrating the solvent effect for the amide
condensation reaction (reaction step 5) as a manufacturing view.

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Materials and methods.

We studied this reaction under various solvents and compared the results.

Typical reaction procedure was as follow ;

(R)-2-Amino-N-[1-(6-methylindol-3-ylmethyl)pyrrolidin-3-yl]acetoamide hydrochloride was dissolved (or suspended) in solvent(s). Triethylamine(3.4mol equivalent) was added. Here were added 5-trifluoromethoxyanthranilic acid(0.9mol equivalent), 1-hydroxy-1,2,3-benzotriazole(1.0mol equivalent) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride(1.1mol equivalent), and the mixture was stirred at 50degree Celsius for 4 hours. After the reaction, ethyl acetate was added to the reaction mixture, and this solution was washed with aqueous sodium hydroxide.

*In the case of using THF as a reaction solvent, THF was evaporated prior to washing with sodium hydroxide.

Then, all solvents were evaporated to get crude targeted compound, (R)

-2-{[2-amino-5-(trifluoromethoxy)phenyl]carbonylamino}-N-[1-(6-methylindol-3-ylmethyl)pyrrolidin-3-yl]acetamide.

Results.

The amount of solvent(s) was about 50mL when 3g of starting material was used in each reaction .

Several solvents were tested in this reaction, and evaluated the reactions in views of yields and purities of the crude compounds and manufacturing processes.

The results are shown in the Table 1.

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Table 1.

<i>Exp. No.</i>	<i>Solvent</i>	<i>Purity(%) HPLC</i>	<i>Yield(%)</i>	<i>Comment</i>
499-015	THF	93.5	89	Unsolved materials Hard to suspend
Yta-1562	THF	92.6	90	Unsolved materials Hard to suspend
499-052	MeOH(11%)/THF	91.7	86	Suspension
499-054	MeOH(20%)/THF	90.5	82	Clear Solution
499-020	MeOH(33%)/THF	91.0	86	Clear Solution
499-064	MeOH	78.9	77	Clear Solution
499-025	2-PrOH	87.5	80	Clear Solution
499-038	AcOEt	46.0	41	Unsolved materials
Yta-1563	MeOH(25%)/AcOEt	93.2	90	Almost Clear Solution
Yta-1559	MeOH(50%)/AcOEt	91.0	87	Clear Solution

At first, THF was used as a solvent in the laboratory studies.

Although the results were good in the cases of using THF as a solvent, there were a lot of unsolved materials in the reaction mixtures and may be hard to suspend them well in the manufacturing scale.

MeOH can be used as a co-solvent in order to get clear solution and be suspended well. But, in those cases, purities and/or yields might be lower than the cases without MeOH.

Only alcoholic solvents, such as MeOH or IPA, can be used as solvents and solutions were clear and well suspended, but purities and yields were low.

On the other hand, as sodium hydroxide washing and extraction must be needed to remove impurities after the reactions, hydrophilic solvents, such as THF and MeOH, must be evaporated prior to washing.

*Small amount of those solvents were OK not to be evaporated.

Then, AcOEt was tested as a solvent in this reaction. But, both purity and yield are very low because of a lot of unsolved materials.

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Again, MeOH can be used as a co-solvent in order to get clear solution and be suspended well. Thus, using 25%MeOH in AcOEt was good for resulting yield and purity.

But, using more amount of MeOH(50%) lead the result decreasing both yield and purity.

Moreover, sodium hydroxide washing can be introduced without any evaporation in this reaction condition.

Conclusions.

We studied the solvent effect for amide condensation reaction (Step 5) using various solvents.

As a conclusion, 25%MeOH in AcOEt can be used in this kind of reaction because of high yield and purity. Moreover, evaporation of reaction solvent is not needed in this reaction condition, so this solvent condition must be promising way for manufacturing procedure.

I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: Oct 1, 2007

Takumi Takeyasu
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